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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,188	SIN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,27-36 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This Action is responsive to Applicant's amendment and remarks filed October 23, 2006. Claims 1-2, 20,23, 30, 32 and 48 have been amended. Claims 23-26, 37-44 have been withdrawn.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and remarks the following rejections have been withdrawn:

(a) the provisional double patenting rejection of claims 1 and 48, page 9, paragraph 6.

(b) the rejection of claims 1 and 48 under 35 U.S.C. 112 first paragraph, page 10, paragraph 7.

(c)

(d) the rejection of claims 1-22, 27-36 and 45-48 under 35 U.S.C. 112, second paragraph, page 10, paragraph 8.

(e)

Rejections Maintained

4. The rejection under 35 U.S.C. 112 first paragraph is maintained for claims 1-22, 27-36 and 45-48 the reasons set forth on pages 3-6, paragraph 4 of the previous Office Action.

The rejection was on the grounds that The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant protein major adhesion protein of *Aeromonas hydrophila* (AHMA) (pQE-AHMA) which corresponds to SEQ ID NO:8 does not reasonably provide enablement for derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila*. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification defines the term "fragments" as any polypeptides with exemplary conservative substitutions in an immuno-interactive polypeptide (page 8). The specification fails to provide a structure for the, derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila.*

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (page 315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila* in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

Applicant's Arguments

Applicant urges that they have amended the claims to remove the derivatives and variants being at least 75% homologous to a said AHMA protein.

Examiners Response to Applicant

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive. Claim 1 recites "immunogenic fragments". The claims encompass fragments of SEQ ID Nos. 2, 4, 6 and 8 and combinations thereof which are not defined. The instant specification has not taught which amino acids are deleted or substituted in the amino acid sequence to arrive at a fragment that is encompassed by the claimed invention.

The claims are directed to an oral vaccine comprising in a orally suitable formulation at least one of isolated recombinant adhesion protein of *Aeromonas hydrophila* (AHMA) selected from the group consisting of isolated recombinant adhesion proteins having the amino acid sequence as set forth in any one of SEQ ID NO:2, 4 or 8 and immunogenic fragments thereof wherein said vaccine is capable by oral administration is an immunologically sufficient amount of effecting immunization of an animal against *Aeromonas hydrophila.*

The specification fails to describe immunoepitopes or fragments that would be protective in Blue gourami as set forth in example VI of the instant specification. The instant specification teaches in Example VI immunization of Blue gourami with recombinant adhesion (pQE-AHMA) which corresponds to SEQ ID NO:8 (pages 16-17). However, these "examples" are not sufficient to provide enablement for the full scope of the rejected claims. The specification is silent as to what specific "immunoepitope" or "immunogenic fragments" confers said a given immune response. Given the lack of guidance contained in the specification and the unpredictability in determining

acceptable sequence variations, one of skill in the art could not make the broadly claimed invention without undue experimentation. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (*Science, 1990, 257:1306-1310)* teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, Greenspan et al. (*Nature Biotechnology 17: 936-937, 1999),* disclose defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here

the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, is only enabling for only the recombinant protein obtained from the pQE-AHMA transformed with *E. coli* used to immunize Glue gourami.

In view of all of the above this rejection is maintain because applicant has not describe specific "immunoepitope" or immunogenic fragments of *Aeromonas hydrophila* recombinant adhesion proteins confers that confer a given protective immune response.

It should be noted that the Bowie and Greenspan references are include to support the Examiner's position and are not to be considered as part of the rejection under 35 U.S.C. 112 first paragraph.

5. The rejection under 35 U.S.C. 102(b) is maintained for claims 1-3, 5-6, 10, 27-29 and 48 the reasons set forth on pages 6-8, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. Fang et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

Applicant urges that Fang et al do not teach an oral composition comprising recombinant protein AHMA. Applicant urges that the route of delivering a vaccine is an important factor for successful immunization. Applicant urges that "oral administration" is more than mere intended use. Applicant urges that the claim limitation "oral" breathes life and meaning into the claims. Applicant refers to Mastroeni et al, 1999 and Boraschi et al, 2003 to support their position. Applicant urges that the composition of Fang et al is structurally and immunologically different from the pure recombinant AHMA that is presently claimed. Applicant urges that Fang et al's composition was extracted from a crude using potassium isothiocynate, a very powerful protein denaturant which is known to disrupt and denature the secondary and tertiary structure

of proteins. Applicant urges that the pure recombinant AHMA is purified as a homogenous pure polypeptide using expression system that expresses the recombinant proteins in a near-native conformation.

Examiners Response to Applicant

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

To address Applicant's comments regarding "routes of vaccine delivery", it should be noted that the claims are directed to a product, a vaccine and not a method of vaccine delivery.

To address Applicant's comments regarding the method used in the prior art to isolated the AHMA protein, it should be noted that the claims are directed to a vaccine and not a method of isolating a protein. It should be noted that the claim limitation "oral" is a limitation of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Applicant has not shown that there is a

structural difference between the vaccine of the prior art as taught by Fang et al and the claimed vaccine composition.

To address Mastroeni et al, 1999 and Boraschi et al, 2003, while it may be true oral immunization is not an easy goal and it has been difficult to elicit strong protective immune responses and IgA production by oral administration, it must be remembered that claimed invention is directed to a product and the route of administering the product or the method of isolating the product does not make a patentable distinction if the products of the prior art and the claimed invention are the same.

In view of all of the above, this rejection is maintained.

6. The rejection under 35 U.S.C. 112 second paragraph is maintained for claim 48 the reasons set forth on page 10, paragraph 9 of the previous Office Action.

The rejection was on the grounds that

Applicant's Arguments

Applicant urges that one of ordinary skill in the art would understand the meaning of the phrase ".predetermined amount". Applicant refers to page 6 and 11 of the instant specification.

Examiners Response to Applicant

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

It is the Examiner's position that the phrase "predetermined amount" is vague and indefinite. The metes and bounds of this phrase cannot be determined because

the amount or range of the "predetermined" amount would change depending on the subject in which it is administered. Thus, this rejection is maintained.

7. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-6, 10, 27-29, 35-36 and 48 the reasons set forth on pages 11-13, paragraph 10 of the previous Office Action.

The rejection was on the grounds that Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139).

Fang et al do no teach palm oil.

Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). Chen et al teach that the present invention provides pharmaceutical oil-in-water emulsion for the deliver of polyfunctional active ingredients (see the Abstract). Chen et al teach that the compositions of the invention that contain organic oils such as palm oil are stable compositions (column 5). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. The claim limitation "...prepared by a method comprising the steps of...".) is being viewed as a process limitation. The products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon.

It would be *prima facie* obvious at the time the invention was made to add the palm oil as taught by Chen et al to the vaccine composition of Fang et al a because

Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). It would be expected barring evidence to the contrary that a vaccine comprising palm oil would be effective stabilizing vaccines at improving delivery of polyfunctional active ingredients.

Applicant's Arguments

Applicant urges that Chen et al that the oil component of the oil-in-water emulsion may not be appropriately polar to effectively incorporate polyfunctional active ingredients at desirable therapeutic level without compromising safety. Applicant teaches that the addition of polarity modifiers to an emulsion can be directly attributed to increasing the polar nature of the oil phase which is said to improve delivery of polyfunctional active ingredients. Applicant urges that one of ordinary skill in the art would not combine the teachings of Fang et al with the palm oil as described in Chen et al without the addition of polarity modifiers.

Applicant urges that there is no suggestion or motivation to combine Fang et al with Chen et al. Applicant urges that Fang et al teach Freund's Complete Adjuvant and Chen describes oil-in-water emulsions. Applicant urges that the two emulsion systems are incompatible. Applicant urges that there is no reasonable expectation of success by one of ordinary skill in the art to provide an orally effective, oral vaccine.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

It is the Examiner's position that Applicant is arguing limitations that at are not in the claims regarding polarity modifiers, desirable, therapeutic level and compromising safety.

In response to applicant's argument that there is no motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the artisan of ordinary skill would be motivated to add palm oil as taught by Chen et al to the compositions of Fang et al because Chen et al teach that organic oil such as palm oil is used to provide improved delivery of polyfunctional active ingredients.

In view of all of the above this rejection is maintained.

8. The rejection under 35 U.S.C. 103(a) is maintained for 7-9 for the reasons set forth on pages 14-16, paragraph 12 of the previous Office Action.

The rejection was on the grounds that Calanchi et al teach binding agents such as carboxymethylcellulose
(column 3). Calanchi et al teach that binders are soluble in water and solvents (column 3). Calanchi et al teach that binders are often used to thicken the composition (column 4).

It would be *prima facie* obvious at the time the invention was made to add carboxymethylcellulose as taught by Calanchi et al to the vaccine composition of Fang et al and Chen et al as combined above because Calanchi et al teach that binders are often used to thicken the composition and have the property of dispersing and dissolving quickly in water or aqueous vehicles (see the Abstract). It would be expected barring evidence to the contrary that a vaccine comprising binding agents such as carboxymethylcellulose would be effective at making the components of the composition easily to disperse and dissolve quickly in water or aqueous vehicles.

Applicant's Arguments

Applicant urges that arguments regarding Fang et al and Chen et al have been described previously. Applicant urges that Calanchi et al teach the use of carboxymethylcellulose as the thickening or suspending agent and not as the binding agent. Applicant urges that Calanchi et al teach away from the claimed invention. Applicant urges that Fang et al either alone or in combination with Chen et al and further in view of Calanchi et al do not disclose each and every limitation found in claims 1 and 48 and claims which are dependent thereof. Calanchi et al do not render claims 7-9 obvious.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

Calanchi et al teach that carboxymethylcellulose is a thickening or suspending agent as well as a water soluble binder. It is the Examiner's position that the combination of references (Fang et al, Chen et al and Calanchi et al) renders the claimed invention obvious.

In view of all of the above this rejection is maintained.

9. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-3, 5-6,10, 15-16, 20-21, 27-36, 45 and 48 for the reasons set forth on pages 14-16, paragraph 12 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al teach a fish vaccine comprising multiple fish antigens (see the Title and the Abstract). Wolf-Watz et al teach that the invention contemplates that the mutant strain of the invention may carry DNA sequences coding for an antigenic determinants from other fish pathogens and is capable of expressing the sequence (column 6). Wolf-Watz et al teach that the invention contemplates vaccines comprising bacteria the carry multiple determinants from different pathogenic fish and capable of expressing hybrid (fusion) determinants (column 7). Wolf-Watz et al teach that viruses such as infectious pancreatic necrosis virus and infectious hematopoietic necrosis virus may apart of the vaccine of the invention (column 6). Wolf-Watz et al teach that the bacteria of the invention contains $1x10^2$-$1x10^8$ bacteria/ml (column 8). Wolf-Watz et al teach that the vaccine of the invention can be added to fish feed (column 8).

Wolf-Watz et al do not teach the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila.*

Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139). The claim limitation "oral" is being viewed as a

limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. The claim limitation "...prepared by a method comprising the steps of...".) is being viewed as a process limitation. The products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon.

It would be *prima facie* obvious at the time the invention was made to add the isolated recombinant adhesin protein from *Aeromonas hydrophila* as taught by Fang et al to the vaccine composition of Wolf-Watz et al because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* and the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* would be effective in protecting against a broad spectrum of fish diseases.

Applicant's Arguments

Applicant urges that as stated above Fang et al disclose a intraperitoneal immunization using the 43 kDA outer membrane protein and does not discloses oral administration. Applicant urges that Wolf-Watz et al teach live, whole cell avirulent strains used as vaccines. Applicant urges that Wolf-Watz et al teaches that love vaccines envoke a stronger immune response than killed pathogens. Applicant urges that there is no motivation or suggestion to combine the Wolf-Watz et al and Fang et al.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

In response to applicant's argument regarding establishment of a *prima facie* case of obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, Wolf-Watz et al teach vaccines comprising *Aeromonas hydrophila*. Wolf-Watz et al do not teach other antigens such as *Ichthyophythirius.* Wang et al teach vaccines comprising *Ichthyophythirius.* The teachings of Fang et al have been described previously. One of ordinary skill in the art would be motivated to combine the teachings of the Fang et al and Wolf-Watz et al because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens. Therefore, a case of *prima facie* obviousness has been established. . It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such as the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process

limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

In view of all of the above this rejection is maintained.

10. The rejection under 35 U.S.C. 103(a) is maintained for claims 11-13 for the reasons set forth on pages 16-17, paragraph 13 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al and Fang et al do not teach the immobilization antigen repeat I of *Ichthyophythirius multifiliis* (FP).

Wang et al teach a vaccine composition comprising the immobilization antigen repeat I of *Ichthyophythirius* and Freund's incomplete adjuvant (see the Abstract). Wang et al teach that fish immunized with the FP antigen developed high titers of serum immobilized antibodies (see the Abstract). Wang et al teach that this study shows there is a clear role for the immobilization antigen repeat I of *Ichthyophythirius* in protection (see the Abstract). The claim limitation "recombinant" is being viewed as a process limitation.

It would be *prima facie* obvious at the time the invention was made to add the immobilization antigen repeat I of *Ichthyophythirius* as taught by Wang et al to the vaccine composition of Wolf-Watz et al and Fang as combined above because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising the isolated recombinant adhesin protein of *Aeromonas hydrophila* and immobilization antigen repeat I of *Ichthyophythirius* would be effective in protecting against a broad spectrum of fish diseases.

Applicant's Arguments

Applicant urges that urges that Wolf-Watz et al teach away from the present claims because Wolf-Watz et al discuss advantages of using whole cell vaccines over killed or isolated recombinant antigens. Applicant urges that Wolf-Watz et al would not lead the artisan of ordinary skill to expect a reasonable expectation of success in providing by oral administration an oral vaccine comprising recombinant protein AHMA

and recombinant protein comprising immobilization antigen repeat of *Ichthyophtirius multifiliis,* inactivated viruses and bacterial antigens or killed bacteria.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

The Examiner disagrees with Applicant's assertion that Wolf-Watz et al teach away from the present claims. It should be remembered that Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens. Wolf-Watz et al teach antigenic determinants in which bacterial pathogens may be derived from (column 6). Thus, Wolf-Watz et al contemplates the use of antigenic determinants or bacteria antigens. There is no limitation in the claims that all antigens used in the claimed vaccine composition are killed. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

In view of all the above this rejection is maintained.

11. The rejection under 35 U.S.C. 103(a) is maintained for claims 22 and 46-47 for the reasons set forth on pages 17-18, paragraph 12 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al and Wang et al as combined above do not teach *Vibrio alginolyticus.*

Morinigo et al teach that a divalent vaccine composition comprising *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida*. Morinigo et al teach that the concentration of protein 800 mg ml^{-1} (page 299).Morinigo et al teach that high protection was conferred by the divalent vaccine (page (302).

It would be *prima facie* obvious at the time the invention was made to add the *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens as taught by Morinigo et al to the vaccine composition of Wolf-Watz et al and Wang et al as combined above because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila,* immobilization antigen repeat I of *Ichthyophythirius,* and *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens.

Applicant's Arguments

Applicant urges that Morinigo et al teach a divalent vaccine composition comprising inactivated and killed whole cell and extracellular products of Vibrio algnolyticus and Photobacterium damselae. Applicant urges that Wolf-Watz et al teaches away from the claimed invention by teaching the advantages of live vaccines over killed vaccines. Applicant urges that Wolf-Watz et al, either alone or in combination with Fang et al, Wang et al and further in view of Morinigo et al do not teach each and every limitations in claims 1 and 48.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

In response to applicant's argument regarding the combination of references Wolf-Watz et al teach vaccines comprising *Aeromonas hydrophila.* Wolf-Watz et al do not teach other antigens such as *Ichthyophythirius.* Wang et al teach vaccines comprising *Ichthyophythirius.* Wolf-Watz et al and Wang et al as combined above do not teach *Vibrio alginolyticus* or *Photobacterium damselae subsp. Piscicida.* Morinigo et al teach vaccine compositions comprising *Vibrio alginolyticus* or *Photobacterium damselae subsp. Piscicida* . One of ordinary skill in the art would be motivated to combine the teachings of the prior art references because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens. Therefore, a case of *prima facie* obviousness has been established.

The Examiner disagrees with Applicant's assertion that the prior art teaches away from the claimed invention. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such as the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

In view of all of the above this rejection is maintained.

Status of Claims

12. No claims allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

Conclusion

14. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
January 30, 2007